MEDICAL STAFF CONFERENCE

The Newer Aspects of Asthma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* The topic today concerns the newer aspects of asthma. The case summary will be presented by Dr. Robert Michael Wilkes.

DR. WILKES:† This was the first admission for this 19-year-old Caucasian woman whose chief complaint was shortness of breath and wheezing. At six months of age the patient had had widespread eczema, followed by an asthmatic attack. Since that time she has been in the hospital seven times for asthma, the last time being one month before the present admission. Three weeks before admission she stopped taking a prescribed daily dose of prednisone. She did well without it for a week, but two weeks before admission she began to have intermittent wheezing, accompanied by a cough productive of yellow sputum, with shortness of breath which became progressively worse.

Past history revealed multiple allergic sensitivities to foods, danders and pollens. Both her father and grandfather had asthma. She was unmarried and seven months pregnant.

On physical examination a blood pressure was 120/60 mm of mercury, pulse rate 120, respirations 28 and temperature 37°C (98.6°F). The chest was clear to percussion. There were bilateral wheezes and rhonchi. The heart was unremarkable. Abdominal examination revealed a seven-month gestation. There was no clubbing, cyanosis or edema of the extremities.

Hemoglobin was 12.6 gm per 100 ml, leukocytes numbered 16,500 per cu mm with 78 percent polymorphonuclear leukocytes, 5 percent eosinophils, 10 percent lymphocytes and 7 percent monocytes. Results of urinalysis were within normal limits. Electrolytes showed a low potassium of 3 mEq per liter. Arterial gases determined during hyperventilation of room air showed a pH of 7.53, pCO_2 of 32 and pO_2 of 80. Forced expiratory volume in one second (FEV_1) was 1100 ml and vital capacity was 1400 ml. X-ray films of the chest were normal, and the sputum contained only normal flora.

In the hospital intravenous fluids and aminophyllin and intermittent positive pressure breathing with isoproterenol were administered. After 48 hours the patient appeared in less respiratory distress, the forced expiratory volume and vital capacity were improved, and the blood gases were normal.

On the fourth day, however, she became very anxious and demanding and threatened to jump out the window. Psychiatric consultation was requested. The day following psychiatric examination her respiratory distress became worse. She began to produce large quantities of yellow sputum. The vital capacity decreased to 900 ml with a FEV_1 of 50 percent. Blood gases showed pO_2 of 68, pCO_2 of 48 and pH of 7.32. Intravenous fluids were increased and hydrocortisone and ampicillin were administered, with dramatic clincial improvement in 40 hours. She was discharged to the medical clinic and is doing well.

DR. SMITH: Thank you, Dr. Wilkes. The chest x-ray film was interpreted as normal and will not be presented. Dr. Warren Gold will com-

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Robert Michael Wilkes, M.D., Resident in Medicine.

ment on this patient and about the newer aspects of asthma.

DR. GOLD:* There have been a large number of advances and changes in the field of asthma in the last five years, including the definition of gamma-E globulin as equivalent to the illusive reagin, the development of quantitative methods of determining the serum levels of gamma-E, the development of *in vitro* tests based on the release of histamine from sensitized leukocytes, the description of several humoral transmitters, and the large amount of work covering newer drugs for therapy, particularly those introduced in the United Kingdom. I will leave these topics for future conferences.

What I would like to talk about this morning is the pronounced increase in the asthma death rate that has been the subject of a large number of recent articles, particularly from the United States, the United Kingdom and Australia. I would also like to comment on some of the newer physiological advances in the field, especially those having to do with the effect of asthma on lung elastic recoil and the role played by the cholinergic nervous system in the regulation of the airways in the asthmatic patient.

Asthma cannot be considered a simple and benign disease. In this country it is now the leading chronic disease in the age group below 18 years. It accounts for approximately 25 percent of grade school and high school absenteeism due to illness in America and causes approximately 7,000 deaths a year.[1] Despite these statistics, a large part of the lay public and even segments of the medical profession consider it a benign ailment. They disregard the fact that any attack of asthma is potentially lethal. Its seriousness is not always recognized by clinical evaluation of the patient. In one study of deaths from asthma (by Speizer and coworkers[2]) 80 percent of the patients died suddenly and unexpectedly; yet in 40 percent of these cases the attending physicians had not considered that the attack was serious at the time they began treating the patient.

As demonstrated by Tai and Read,[3] this paradox is partially attributable to the serious abnormalities in blood gases that can accompany even a mild asthmatic attack. In that study, all patients were thought to have mild asthma, not serious enough to require hospital admission; yet 14 of these patients had arterial O_2 tensions below 60 mm of mercury and four of the 14 had arterial CO_2 above 45 mm of mercury. Although there was a slight tendency for the more seriously obstructed patients to have the lower pO_2, a significant number of those with forced expiratory volumes above one liter had decreased values of arterial oxygen tension.

The degree of hypoxemia observed in the study by Tai and Read is not necessarily a threat in itself, but it makes the patient extremely vulnerable to any slight change in the status of his airways. The development of mucus plugs or infection or more bronchoconstriction can put the patient in a much more serious situation. The asthmatic patient is really sitting on the "knee" of his hemoglobin oxygen saturation curve; and when he has a pO_2 of 60 mm of mercury, a further decrease in pO_2 will produce a serious drop in the level of oxygen saturation with potentially lethal consequences. These same investigations showed that the pCO_2 in asthmatic patients may be increased as well; nine patients had pCO_2 above 45 mm of mercury.

Another point to be considered from these data is the fact that screening tests which are based on the bloodless, rebreathing measurement of pCO_2 are no reassurance that arterial pO_2 is normal; only four of the patients with hypoxemia had elevated pCO_2. In light of these data it is not surprising that in patients with asthma serious hypoxemia may suddenly develop with only slight exacerbations of their illness.

The other point I would like to emphasize from from these data is well illustrated by the patient presented today. The determination of respiratory insufficiency is a laboratory diagnosis which requires arterial blood determinations. You cannot tell by looking at the patient whether or not the blood gases are normal. Perhaps these abnormalities in arterial blood gases may be partially responsible for the increased mortality rate ascribed to asthma in young people reported from different parts of the world.

Some of the other possible causes of this in-

*Warren M. Gold, M.D., Assistant Professor of Medicine.

TABLE 1.—Possible Causes of the Increased Death Rate in Asthma

Change in nature of disease
Atmospheric pollution
Infection
Pitfalls in therapy
Cardiac failure
Emphysema

creased asthma death rate are listed in Table 1. One factor to be considered is a possible change in the nature of the disease. However, when you compare the pathological reports describing patients dying now with the pathological reports of 20 to 30 years ago, there is no evidence of a change in the underlying pathologic changes of the disease. Airways are obstructed by mucus plugs as well as smooth muscle spasm and inflammation of the airway walls.[2]

Atmospheric pollution is a very potent factor that has to be considered, particularly for those of us living in a state where we are warned by announcements on television and radio to avoid heavy exercise on days when air pollution is increased. I think there may be a pathogenic relationship between the asthma death rate and atmospheric pollution; however, there is no good epidemiological data comparing death rates from asthma in regions with and without pollution.

In a Los Angeles study of children dying with asthma, infection was a very common cause of death.[4] The possible relationship between the widespread use of antibiotics, corticosteroids and deaths by infection must certainly be considered in the management of every patient.

There are numerous pitfalls in the management of asthmatic patients. In the Los Angeles study, aminophyllin toxicity in children caused by excessive use of aminophyllin suppositories, was an important factor.[4] The counterpart is the asthmatic adult who is given undiluted, rapid infusions of aminophyllin, develops hypotension and cardiac arrhythmia and dies soon thereafter. Sedation can also be extremely dangerous when administered to an asthmatic patient who is agitated and restless and complaining (note that the patient under discussion was "wanting to jump out the window") because of the central nervous system effects of hypoxemia. Whenever a patient is restless and agitated, an arterial needle should be inserted in the arm and the pO_2 measured before a sedative is administered. A number of asthmatic patients have died because sedative drugs were given when they were severely hypoxemic.

Corticosteroids, as I have already indicated, may be associated with infection in asthmatic patients. More important perhaps is the need for early use of corticosteroids in a patient with severe asthma who has taken the drugs recently. The patient under discussion had stopped the steroids three weeks before hospital admission, and had been receiving continuous daily steroid therapy before then. Clinical improvement did not begin until after the fourth day of hospital stay when corticosteroids were finally added to the treatment program.

I would like to turn to the possible role of pressurized bronchodilator aerosol overdosage in the increased asthma death rate. This factor has received a great deal of attention lately, particularly in the United Kingdom.[2,5,6,7] In fact, *Lancet* has had a number of articles within the last two years on the asthma death rate and on the possible relationship to pressurized bronchodilator aerosols. In the most recent lead article,[7] the editors stated that, in England at least, there appeared to be a direct cause-and-effect relationship between pressurized isoproterenol aerosols and the excessive death rate. In 1959 the death rate secondary to asthma was approximately 1200; in 1966 it was doubled. Between the ages of 5 and 34, the death rate in England increased two and a half times during this period. From the ages 10 to 14, the death rate increased almost seven times. In this latter age group, asthma became the fourth most common cause of death, ranking behind motor vehicle accidents, cancer and respiratory tract infections. During this period, Inman and Adelstein[6] showed a statistical correlation between the asthma death rate and the sales and prescriptions of bronchodilator aerosols. It should be noted that in the United Kingdom it was possible up until December of 1968 to buy bronchodilator aerosols over the counter without prescription. In England the concern about the increased death rate led to warnings by the Ministry of Health and passage of legislation which stopped the marketing of these drugs without prescription. Statistical analysis suggests a pronounced decrease in the asthma death rate in the first quarter of 1969, although this decrease in death rate was greater than the decrease in the use of nonprescription

drugs. The statistics seem to indicate that if there is a cause-and-effect correlation in England, it appears to be between over-the-counter, nonprescription drug sales and the excessive death rate.

If there is a cause-and-effect relation of bronchodilator aerosols to death rate, what can the mechanism be? (1) The aerosol generators that are used today are much more efficient than they used to be, it is possible that the patient who was accustomed to a hand-squeeze-bulb is now getting a much larger dose more efficiently deep down into the lung than previously. (2) It has also been suggested that isoproterenol itself can induce bronchial constriction.[8] There are a number of case reports suggesting this possibility. From my review of these papers, I think the evidence for this mechanism is not convincing. (3) A possible relationship between the bronchodilators and hypoxemia has been emphasized in at least a dozen papers in the English language since the middle 1960's.[9] In one such study by Knudsen and Constantine[9] the authors gave isoproterenol aerosol to healthy subjects and asthmatic patients and measured their airway resistance. The results showed that the airway resistance decreased after the isoproterenol aerosol. Although the arterial pO_2 in the normal subjects did not change or increased slightly, the arterial pO_2 in asthmatic patients decreased. There was no change in the alveolar pO_2 so that large differences developed between alveolar pO_2 and arterial pO_2 in all asthmatic patients. Subsequently other reports have indicated that isoproterenol by aerosol, aminophylline and epinephrine parenterally, and a number of others of the commonly used sympathomimetic agents will cause a slight decrease in arterial pO_2.

The average decrease in pO_2 in most of these studies is of the order of 5.0 mm of mercury. It is a very small change, interesting physiologically, but clinically probably not too important as a cause of the increased asthma death rate. It is important therapeutically in the sense that although we may be improving the airway resistance in these patients, we may not be improving their level of oxygenation, and added oxygen in the inspired gas may be needed.

There are two mechanisms suggested for these changes in oxygenation. One is that the aerosol is being delivered to the well-ventilated portions of the lung. These units then become better ventilated at the expense of the obstructed, poorly ventilated units, this causing further exacerbation of regional hypoventilation relative to perfusion, and the pO_2 drops slightly. The alternate explanation for the decrease in arterial pO_2, particularly with the parenteral agents, is that the vasodilating effect of these sympathomimetics causes an increase in perfusion to the poorly ventilated units. This increased perfusion would exacerbate the regional hypoventilation of those poorly ventilated but perfused units, and the arterial pO_2 would decrease. The fact that this change in oxygenation is small and that it can be observed with the old standbys of asthma treatment like aminophylline and epinephrine, even when used parenterally, suggests that this mechanism cannot account for the increased asthma death rate.

The British particularly have suggested another possible mechanism implicating bronchodilator aerosols. They suggest that young asthmatics in England "who are dying at home clutching their empty bronchodilator cannisters" are being intoxicated by isoproterenol-induced, beta-adrenergic stimulation of the heart, and are dying of cardiac arrhythmia.[7] On the other hand, there are reports that with heavy use of bronchodilators, both normal and asthmatic persons have a reduced heart rate response to test-infusions of isoproterenol. Furthermore, it is suggested that this reduced heart rate response is related to a breakdown product of isoproterenol which has been found in man—3-methoxyisoproterenol, a beta-adrenergic blocking agent. It is possible that this metabolite might indeed be helping to protect these people against the cardiac toxicity of the drug.[10]

I think it is still an open question whether there is some effect of bronchodilator aerosols that is responsible for the increased asthma death rate in England. In America the problem appears to be quite different in many ways. In addition to the possible roles of infection and atmospheric pollution, our patients are dying in hospitals, not at home. In hospitals, many pitfalls in management are possible. Besides the several that I have already mentioned, another important problem in management to be considered is the use of controlled ventilation in these patients. At Children's Hospital in Boston,

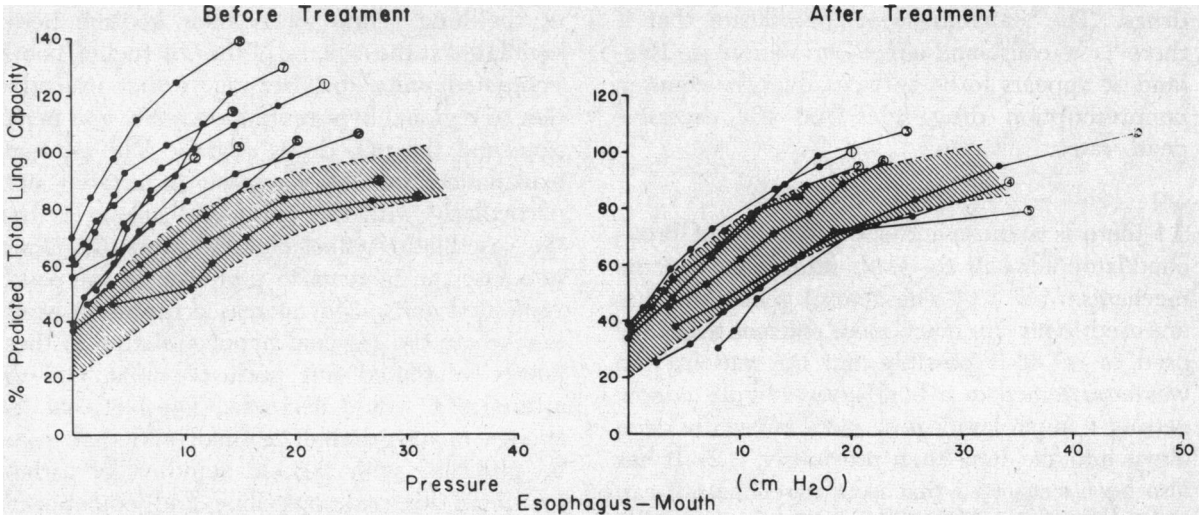

Chart 1.—Effect of treatment on the elastic recoil curve of the lungs in asthma. The curves on the left were obtained in ten untreated patients. The curves on the right were obtained after treatment with bronchodilator therapy and corticosteroids in seven patients. The circled number at the end of each curve is the patient number. The shaded zone represents the ±2 standard deviation (SD) for the lung elastic recoil curves of 21 healthy controls in the same age range. (Reprinted with the courtesy of the publisher from Gold *et al*, J Appl Physiol, 1967, reference 12.)

I reviewed 16 deaths in asthmatic patients in a three-year-period and found that in six of these cases death was due to the failure to evaluate the arterial blood gases until cardiac arrest or respiratory arrest had occurred. In ten of them death was the result of problems with controlled therapy. In many institutions patients in status asthmaticus who develop respiratory insufficiency are paralyzed with curare compounds, sedated and treated with constant volume ventilators. This is a very risky treatment. Endotracheal tubes can come out; the patient can become uncoupled from the ventilator; the ventilators may not function properly, and death can result.

Cardiac failure has been suggested as a possible factor, but it is extremely rare. The only patient I have seen with cardiac failure was given excessive levels of bicarbonate without a monitoring of his acid-base status.

The possibility that chronic asthma may lead to destructive changes in the pulmonary parenchyma with alteration in the elastic properties of the lung (emphysema) has been suggested as a possible explanation for the increased death rate. I have been very much interested in this possibility and would have said five years ago that asthma never causes emphysema. Now I am not so certain. In 1958, when the Cardiovascular Research Institute first opened here, Dr. William Tooley[11] concerned himself with this problem and studied ten patients with severe asthma of at least seven years' duration. He showed, as have a number of other workers, that you could completely correct all evidence of airway obstruction by intensive treatment. It is interesting that he found three of these patients who still had overinflated lungs after treatment. (They had abnormal increases in residual volume and functional residual capacity.) He postulated that these changes might have been due to the chest wall having been inflated for so long that it stayed expanded and passively overinflated the lungs. I reviewed this paper and postulated that the lung elastic recoil might be abnormal in these patients and account for the persistent overinflation observed by Dr. Tooley.

We studied a group of asthmatic children (including six of the patients originally studied by Dr. Tooley) and measured their lung elastic recoil.[12] Chart 1 shows the elastic recoil pressure and lung volume expressed as a percent of predicted total lung capacity. The shaded zone on the chart is the normal range for age-specific controls, since lung elastic recoil normally decreases with age. A number of these children had a loss in lung elastic recoil. The curves are shifted to the left of the normal curve, and the maximal pressures are reduced. The children were then treated and in the same chart are shown the elastic recoil curves which are all

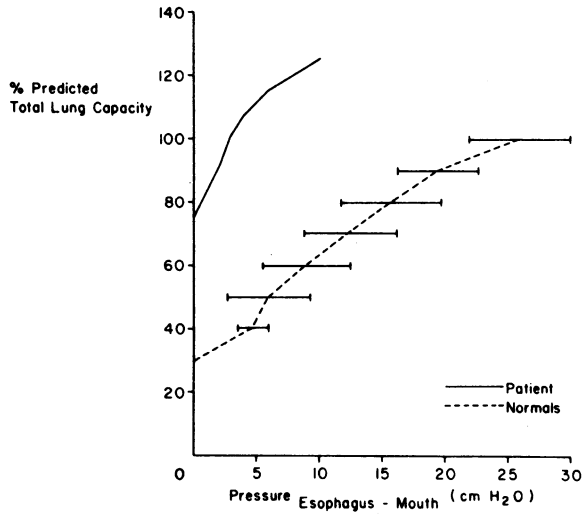

Chart 2.—Lung elastic recoil in severe, young asthmatic patient. The solid line indicates the curve obtained in the patient. The distal line indicates the curve (mean ±1 SD) obtained in age-specific healthy controls.

shifted back within normal range. This study was the first demonstration that with a respiratory illness there may be a reversible, transient loss of elastic lung recoil. The mechanism is still unknown. We tried to duplicate this change by inducing acute bronchoconstriction in asthmatic persons and healthy subjects, and also by overinflating the chests of healthy subjects. No changes in lung elastic recoil occurred during the time period of the study.

In this institution we recently studied a nine-year-old child who had had chronic asthma since one year of age. Chart 2 shows this patient's lung elastic recoil curve. The curve is plotted against control values for his age. It looks like a curve of a patient with emphysema. The maximal pressure is only 10 cm of water; the curve is very steep; and there is a definite shift to the left. I do not know the underlying disease state in this case or whether intensive treatment will make this patient's lung function normally. When this observation is coupled with the recent report by Finucane and Colebatch[13] that lung elastic recoil may not return to normal in asthma despite almost four months of intensive treatment, one wonders what the underlying structural changes in such lungs might be. It is necessary to review the question of whether chronic asthma can produce lung changes of a permanent nature.

There is some exciting work at this institution that Dr. Jay Nadel[14] and coworkers have done implicating the cholinergic nervous system in the hyperresponsiveness of the asthmatic patient. It has been shown previously in animals that irritation of conducting airways with catheters, sulfur dioxide, chemically inert dusts or cold air can produce cough and reflex bronchoconstriction. The responsible receptors appear to be in the airways. They are called subepithelial irritant or cough receptors, and the afferent and efferent pathways appear to be in the vagus nerves. A large number of stimuli such as cold air, dust, mechanical irritation, citric acid, histamine, and infection-forced expiratory and inspiratory maneuvers can elicit this cough and bronchoconstriction. Similar stimuli in healthy humans have been shown to produce similar changes. In animals and in humans pretreatment with atropine will block the bronchoconstriction, but not the cough. This fact suggests that the atropine is working on the efferent pathway.

It is possible to sensitize these receptors by exposing animals to ammonia gas or infection. These receptors will then fire off at a lower dose of the stimulus and with a more profound bronchoconstriction than they did before sensitization. The same sequence of events occurs in humans. Dr. Nadel has proposed that the increased responsiveness of the airways in these patients is due to sensitization of these irritant subepithelial cough receptors.

This is an important concept and a useful one for a number of reasons. For example, the most common time at operation to induce asthma in the asthmatic patient is when you intubate the airway. The same procedure is followed with the asthmatic patient when bronchography or bronchoscopy is performed. In non-asthmatic subjects, airway irritability may develop in association with certain upper respiratory tract infections, resulting in cough and bronchoconstriction which can be blocked by atropine. Perhaps in so-called "infectious asthma" these patients may not have a specific antigen-antibody reaction to the bacterial antigen but may have nonspecific stimulation of the irritant receptors of the airway causing bronchoconstriction.

Finally, this concept suggests that global therapy must be designed for the management of the patient with asthma. The physician who relies only on immunotherapy, environmental

control, pharmacotherapy, or psychotherapy may not be able to control the asthma. Instead of concentrating all efforts in one approach while neglecting all others, proper management would require the appropriate use of all means (immunotherapy, environmental control, pharmacotherapy and psychotherapy) on the individualized basis. However, once the bronchoconstriction occurs (whether it is due to a psychic effect or allergenic effect) bronchodilator therapy is required.

Dr. Smith: Thank you very much, Dr. Gold. Are there any questions or comments?

Question: Is there any place for the use of atropine in the treatment of a patient in an established attack?

Dr. Gold: What we have discussed so far is interesting physiologically, but it should not be applied in any kind of general way in the treatment of patients. There is the risk, obviously, that atropine has a drying effect on the airways. Mucus plugs appear to be the major problem in patients in status asthmaticus, so I would caution you against running out tomorrow and treating all your asthmatic patients with atropine. However, we have had a patient in the last year who was responding poorly to the usual therapy; she was successfully treated with atropine, using only 0.3 mg intravenously.

Comment: Perhaps the way the aerosols are working to the detriment of the patient is through the sensitized system of irritant receptors, and when the patient is hyperresponsive the particles of the propellant are inducing bronchoconstriction.

Dr. Gold: It is a good idea, but I think most of the studies that have been done on the propellants in patients with asthma indicate that they are not inducing bronchoconstriction. However, related to the question of particle-induced-bronchoconstriction is the question of the use of the ultrasound nebulizers in asthma therapy. There is reasonable evidence that you can induce bronchoconstriction with the particles of water generated by the ultrasound nebulizers, so I would be very careful to individualize the use of ultrasonic nebulizers in treating asthmatic patients.

REFERENCES

1. Schiffer CG, Hunt EP: Illnesses among children. Children's Bureau Publication, Washington, 1963 p. 14
2. Speizer FE, Doll R, Heil P: Observations on recent increase in mortality from asthma. Brit Med J 1: 335-339, 1968
3. Tai E, Read J: Blood gas tensions in bronchial asthma. Lancet 1: 644-646, 1967
4. Richards W, Patrick J: Deaths from asthma in children. Amer J Dis Child 110: 4-21, 1965
5. Lead article: Death from asthma. Lancet 1: 1412-1413, 1968
6. Inman WHW, Adelstein AM: Rise and fall of asthma mortality in England and Wales in relation to the use of pressurized aerosols. Lancet 2: 279-285, 1969
7. Lead article: Aerosol bronchodilators and asthma mortality. Lancet 2: 305-307, 1969
8. Keighley JF: Iatrogenic asthma associated with adenergic aerosols. Ann Intern Med 65: 985-995, 1966
9. Knudson RJ, Constantine HP: An effect of isoproterenol on ventilation-perfusion in asthmatic versus normal subjects. J Appl Physiol 22: 402-406, 1967
10. Patterson JW, Conolly ME, Davies DS, *et al*: Isoprenaline resistance and the use of pressurized aerosols in asthma. Lancet 2: 426-429, 1968
11. Tooley WH, DeMurth G, Nadel JA: The reversibility of obstructive changes in severe childhood asthma. J Pediat 60: 517-524, 1965
12. Gold WM, Kaufman HS, Nadel JA: Elastic recoil of the lungs in chronic asthmatic patients before and after therapy. J Appl Physiol 23: 433-438, 1967
13. Finucane KE, Colebatch HJH: Elastic behaviour of the lung in patients with airway obstruction. J Appl Physiol 26: 330-338, 1969
14. Simonsson BG, Jacobs FM, Nadel JA: Role of the autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. J Clin Invest 45: 1812-1818, 1967

ESTROGEN DOSAGE IN THE MENOPAUSE

"There are two major considerations in the use of estrogens in the menopausal woman: first, that the dose employed be the smallest available to assuage the woman's symptoms; and second, that it be given for prescribed periods of time in some form of cycle and that it never be given without the control of a physician. When this is accomplished, there is no question that estrogen relieves, estrogen helps, and up to now . . . I have seen no harm in the properly selected patient."

—S. LEON ISRAEL, M.D., Philadelphia

Extracted from *Audio-Digest Obstetrics and Gynecology,* Vol. 16, No. 12, in the Audio-Digest Foundation's subscription series of tape-recorded programs.